REMARKS

By an Office Action dated July 28, 2004 in the file of the above-identified application, the Examiner rejected the application one more time based on obviousness of claim subject matter. Based on this submission, reconsideration of the merits of this patent application is respectfully requested.

The applicants wish to thank the Examiner for reconsidering the issues that were present after the last response in this application. All §112 issues are now resolved, and the sole remaining issue in this case is a rejection for obviousness under 35 U.S.C. §103 over Twisk et al. in view of Teasdale and Jackson as well as a prior patent to Attie et al. Based on the comments presented below, the applicants respectfully request that the Examiner reconsider the merits if this obviousness rejection.

It is the position of the applicants here that the success of the method and product as taught by this application was not predictable from the cited prior art. Since there was not a "reasonable expectation of success" as required to sustain a rejection for obviousness under 35 U.S.C. §103 in a biotechnology case, it is submitted that the rejection should be withdrawn. The applicants wish to present here, one last time, arguments why this subject matter is not obvious over the cited prior art, so that it may be considered by the Examiner one more time to hopefully persuade the Examiner of the non-obviousness of this subject matter.

The applicants submit that there were multiple uncertainties in trying to attempt the achieve the result that the applicants have demonstrated in their experimental examples contained with the application that they have achieved. Lowering serum cholesterol levels is a highly desirable result which has been sought by many means. It is submitted that the cited prior art does not demonstrate that this result could actually be achieved by the method attempted by the applicants here.

It is true that the soluble form of the LDL receptor was in the prior art, as exemplified in the prior Attie et al. patent. It is also true that the LDL receptor had been linked to apoB secretion in the recently published Twisk et al. paper authored, in part, by some of the inventors of this patent application. It is also true, that certain peptide markers or motifs, notably KDEL, have been identified as signal peptides which can cause proteins to which they are tagged to be sequestered in the endoplasmic reticulum. However, the applicants submit that these teachings, when taken in the context of their certainties and uncertainties, do not make obvious that the experiment as conducted by the applicants here would actually work to lower serum cholesterol levels in individuals. Perhaps this argument can best be

understood by pointing out some of the uncertainties inherent in this process, and why the result was uncertain before the applicants obtained the proof that they have disclosed here.

The paper by Teasdale and Jackson does recite that some proteins tagged with the receptor KDEL or other signals tagged for the endoplasmic reticula, are retained as endoplasmic reticulum by virtue of the signal peptides. However, it is far from clear that this phenomenon would be effective for all proteins, particularly for non-native proteins. Teasdale and Jackson specifically report that chimeric molecules tagged with KDEL are often modified by the golgi enzymes (page 40 of the article) where endogenous proteins having such signal peptides are not modified in this way. Note that the molecule here, a truncated and soluble LDL receptor to which a signal peptide has been attached, is a nonnative protein and could not be considered endogenous in this form. Therefore it was not predictable in advance whether or not that chimeric protein molecule would be modified by the golgi apparatus of the cell.

It is also well known that proteins are highly complex three dimensional structures. Whenever one adds an additional domain to a protein or a signal peptide, the complete success and functionality of that molecule cannot be predicted in advance. The LDL receptor 354 protein had previously been described as being highly soluble (Attie, U.S. Patent No. 5,521,071). It was not clear that the fusion created by the LDLR 354 protein and the KDEL signal peptide would, as hoped, be aggregated in the endoplasmic reticulum and be sequested in a form in which the binding site for the receptor would be available for binding to apoE in that reticulum. While the Teasdale and Jackson paper may suggest that some proteins with the signal would attach to the endoplasmic reticulum, it was not clear that the attachment would leave the soluble receptor in a form and orientation so that binding to apoE would still occur.

It was not clear prior to the work described here that the endoplasmic reticulum was the right place in the secretion pathway in which to trap apoB. The secretion of apoB is admittedly a complex procedure. It was not clear before the work described here whether the receptors would be overwhelmed or presented in sufficient amount or if other mechanisms would permit apoB secretion when the truncated receptors were expressed in mammalian cells. In other words, while the applicants had the hope that truncated LDL receptor in the ER would trap apoB, it was not at all clear that this strategem would be sufficient or effective by itself and not evaded by some other cellular mechanism.

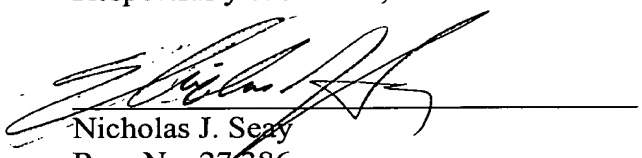
As mentioned, it was also not clear that the soluble LDL receiver would still function if trapped in the endoplasmic reticulum to bind and destroy apoB. Did the binding require a geometry not available in the ER?

Lastly, as the Examiner argued earlier in the file of this application, genetic engineering of animals or humans is a process that is not readily predictable and which often fails. As the Examiner noted, many experiments fail to achieve the desired result. If the applicants had filed a prophetic case on this concept, the Examiner would rightly have demanded evidence that the idea would work before granting that the claimed method was enabled. It was not clear prior to the work of the applicants here that the described expression cassettes could be expressed in animals to result in meaningful levels of protein or, if that the fusion proteins were expressed, that they would appropriately sequester apoB and prevent its secretion, again in sufficient amount to be measurable. The examples as presented here demonstrate that a single vector introduced into the vein of an animal can result in lower LDL levels in the blood stream of that animal. The experiments worked in spite of the uncertainties involved in conducting these tests, but the success of this strategy could not fairly have been predicted from the prior art due to these uncertainties.

For these reasons, the applicants believe that the success of this work described in this patent application was not predictable in advance and that therefore the method claims of this application were not obvious in view of the cited art since there was not a reasonable expectation of success.

Accordingly, a reconsideration of the merits of this patent application is respectfully requested.

Respectfully submitted,



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